diagnosis is still problematic. Effective causal treatment is available only for infections with *B. burgdorferi* and HGE. By contrast, primary prevention by immunization is at hand against arboviruses only. The efficacy of vaccines against *B. burgdorferi* recently studied in the USA has yet to be determined in Europe.

S179 Hemolytic uremic syndrome

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Postenteropathic hemolytic uremic syndrome (HUS) is preceded by diarrhea or hemorrhagic colitis and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. It has been associated with enterohemorrhagic *Escherichia coli* (EHEC) isolated from patients during large food- and water-borne outbreaks. The bacteria produce several well-characterized virulence factors such as: Shiga toxin (Stx) which is cytotoxic to human renal endothelial and epithelial cells and rabbit intestinal epithelial cells; intimin, an outer-membrane protein, which mediates intimate intestinal colonization, and its receptor, *E. coli* secretory protein EspE, which is transferred from the bacteria to the eukaryotic cell; Esps A, B and D, which activate the signal transduction events necessary for the formation of intestinal attachment and effacement lesions; and lipopolysaccharide. Both lipopolysaccharide and Stx-2 are important for disease development in a mouse model of EHEC infection. Mice develop gastrointestinal, neurologic and systemic symptoms, glomerular and tubular apoptosis, necrotic and apoptotic foci in the colon and fragmented erythrocytes. These aspects of disease resemble human HUS. Even mice inoculated with EHEC strains that do not produce intimin or Esp A and B develop similar symptoms and pathology. Children with HUS mount an antibody response to intimin, Esp A and Esp B which may be useful for detection of EHEC infection. Infected children also secrete large amounts of interleukin-6 in their urine. Stimulation of pediatric renal tubular cells with Stx leads to the secretion of large amounts of interleukin-6, which may play a role in the host response to EHEC infection.

New developments in treatment of respiratory tract infections

S185 Antimicrobial spectrum of moxifloxacin

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Moxifloxacin is a new 8-methoxyquinolone that is highly effective against all predominant respiratory pathogens, including: Gram-positive (i.e. *Streptococcus pneumoniae),* Gram-negative (i.e. *Haemophilus influenzae* and *Moraxella catarrhalis)* and atypical (i.e. *Chlamydia pneumoniae* and *Legionella pneumophila)* bacteria. In contrast to fluoroquinolone agents, which showed greater Gram-negative than Gram-positive activity, moxifloxacin has been shown to be highly active against S. *pneumoniae,* including penicillin-resistant strains (MIC_{90}s 0.06–0.12 mg/L) while retaining excellent Gram-negative activity (MIC_{90}s for *H. influenzae* and *M. catarrhalis* (including beta-lactamase-producing strains) <0.12 mg/L). Several studies of dissociated fluoroquinolone resistance have shown that moxifloxacin may have a lower potential than other quinolones to induce bacterial resistance. This phenomenon may be attributable to moxifloxacin's high intrinsic activity for two intracellular targets: DNA topoisomerase IV (Gram-positive organisms) and DNA gyrase (Gram-negative organisms). Addition of a methoxy group to N1-cyclopropyl fluoroquinolones improves lethal activity. Consequently, C8-methoxy derivatives, such as moxifloxacin, restrict the acquisition of resistance by bacterial populations; moxifloxacin retains high activity against first- and second-step ciprofloxacin- and ofloxacin-resistant mutants. Hence, the employment of moxifloxacin for the management of respiratory tract infections may be ecologically preferable, since its high in vitro potency and reduced propensity to elicit bacterial resistance may curtail the spread of resistant strains. This presentation will review the in vitro profile of moxifloxacin versus other fluoroquinolones and conventional first-line agents for the management of community-acquired respiratory tract infections.

S186 Pharmacokinetics and pharmacodynamics

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Pharmacokinetic and pharmacodynamic data for antibacterial agents can be integrated into several ratios, including: (1) the area under the concentration–time curve (AUC) to the minimum inhibitory concentration of the pathogen (AUC/MIC) or AUIC (which is the AUC/MIC normalized for 24 h), and (2) the peak serum concentration (C_{max}) to the MIC (C_{max}/MIC). With other quinolones, AUIC values above 125 and C_{max}/MIC ratios of 8–10 have been associated with optimal antibacterial activity. Lower values may relate to less rapid bactericidal activity and the selection of resistant bacteria. This target AUIC may be achieved with a single antibiotic or it can be the sum of AUIC values of two or more antibiotics. There is considerable variability in the actual AUIC value for patients when antibiotics are given in their usually recommended dosages. The achievement of minimally effective antibiotic action, consisting of an AUIC above 125, is associated with bacterial eradication in about 7 days for beta-lactams and quinolones. When AUIC is increased to 250, the quinolone ciprofloxacin (which displays in vivo concentration-dependent bacterial killing) can eliminate the bacterial pathogen in 1–2 days. Beta-lactams, even when dosed to an AUIC of 250, often require longer treatment duration to eliminate the bacterial pathogen, because the in vivo bacterial killing rate is slower with beta-lactams than with the quinolones. This remains true even at AUIC values of 250 for both compounds, which is theoretically identical dosing. The new 8-methoxyquinolone agent moxifloxacin has been shown to reach AUIC and C_{max}/MIC_{90} values considerably greater than the ideal values of 125 and 12, respectively, that are necessary to effect rapid eradication of potential pathogens. The C_{max} long half-life (10–12 h) and inherent in vitro antibacterial activity against a broad range of pathogenic bacteria suggest that moxifloxacin will be useful for the treatment of a variety of respiratory tract and other infections.

S187 Bronchitis overview

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Acute exacerbations of chronic obstructive pulmonary disease (COPD) are common, as a reason for both general practice consultations and hospital admissions. They have a major impact on patients' quality of life, which may take up to 6 weeks to return to baseline. Bacterial infection of the respiratory mucosa occurs in at least half of the cases. This attracts an inflammatory response which may clear the infection. Spontaneous resolution is less likely to occur

in patients with impaired lung defenses, and established infection may lead to deterioration in already borderline lung function or in a co-morbid condition. Some patients also harbor bacteria in their airways when in a stable condition, and this stimulates chronic inflammation. We do not know whether chronic infection contributes to decline in lung function, or to the frequency of exacerbations. Significant benefit from antibiotics has been demonstrated in patients with moderate to severe exacerbations defined by increased dyspnea, sputum production and sputum purulence. The prevalence of resistance to commonly prescribed beta-lactam and macrolide antibiotics in the bacterial pathogens causing exacerbations has increased. Antibiotics should be targeted at those patients with more severe exacerbations and risk factors contributing to poor outcome; treatment is usually empirical and new agents, such as moxifloxacin,. are more successful in terms of bacteriologic eradication. Future studies should compare new and standard agents in patients with more severe disease, and consider using new modes of evaluation.

S188 Sinusitis overview

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Introduction: Acute sinusitis is associated with significant morbidity and represents an important cause of primary care practitioner consultation. The primary cause of acute sinusitis is viral or bacterial infection. In recent years, there has been a significant increase in resistance rates in the major causative bacterial pathogens of acute sinusitis (i.e. *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*); hence, it is important that new agents are available to provide broad and potent empirical coverage of all possible causative pathogens. Moxifloxacin is a novel 8-methoxy-quinolone with excellent in vitro activity against *all* potential respiratory pathogens and a good pharmacokinetic/pharmacodynamic profile. Moxifloxacin has been shown to achieve rapid and high penetration (with levels several-fold in excess of the MIC_{90}s of the causative pathogens of sinusitis for at least 36 h post-dosing) into the sinus tissues following oral, 400-mg doses.

Methods: This presentation will review data from a recent meta-analysis comparing the results of four multinational clinical trials in patients with acute sinusitis treated with either 400 mg of moxifloxacin or a comparator (cefuroxime).

Results: The meta-analysis revealed that the mean eradication rate for all isolates combined (96%) is in accordance with the high clinical efficacy of moxifloxacin (96% resolution/improvement). The bacteriologic etiology for cefuroxime-treated patients was comparable to that of the moxifloxacin-treated population, with slightly lower resolution/improvement (90%) and eradication (93%) rates for cefuroxime. The modal moxifloxacin MIC was 0.25 mg/L for *S. pneumoniae*, 0.064 mg/L for *H. influenzae* and 0.125 mg/L for *M. catarrhalis.*

Conclusions: Moxifloxacin was highly successful, in terms of both clinical efficacy and bacteriologic eradication rates, in the treatment of acute sinusitis.

S189 Safety profile of moxifloxacin

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Moxifloxacin is a new 8-methoxyquinolone with excellent in vitro Gram-positive and Gram-negative activity and a promising pharmacokinetic/pharmacodynamic profile. This presentation will summarize the current knowledge surrounding fluoroquinolone toxicity and will review the results of a recent meta-analysis of the moxifloxacin clinical safety database comprising a total of 20 phase II and III trials.

Data from 4926 patients with exposure to moxifloxacin and 3415 patients with exposure to comparators revealed that the incidences of adverse drug reactions (ADRs) were comparable among all treatment groups. The majority of ADRs were mild and transient, and no unexpected severe reactions occurred. The overall ADR discontinuation rate observed with moxifloxacin was 3.8%. The most frequently reported adverse events in patients treated with moxifloxacin were nausea (7.2%) and diarrhea (5.7%) with low discontinuation rates (0.8% and 0.5% respectively); dizziness was reported by 2.8% of patients (discontinuation rate 0.5%). Moxifloxacin is a photostable fluoroquinolone and there was no drug-related case of phototoxicity.

As is the case with all new drugs, at present no clear-cut statement can be made about rarely occurring adverse reactions (at incidences of $<0.1\%$). However, analysis of this rather large clinical database indicates that the safety and tolerability profile of moxifloxacin compares favorably with other quinolones recognized to be well tolerated (e.g. ciprofloxacin).

Molecular methods in the diagnostic laboratory: when to start and where to stop

S193 Bias associated with discrepant analysis

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The purpose of this presentation is to show that the sensitivity and specificity estimates obtained by 'discrepant analysis' are upwardly biased. Discrepant analysis is a widely used technique that attempts to provide estimates of sensitivity and specificity in the presence of an imperfect gold standard. Discrepant analysis has been used in the evaluation of *Chlamydia trachomatis, Neisseria gonorrhoeae, Clostridium difficile, Mycobacterium tuberculosis, Legionella* species, *Toxoplasma gondii, Helicobacter pylori*, etc. This technique has been applied by many researchers to estimate the sensitivity and specificity of DNA-amplification tests such as the plasmid-based ligase chain reaction (LCR) and polymerase chain reaction (PCR) tests. Moreover, earlier package inserts of some of the DNA-amplification tests contain estimates of sensitivity and specificity based on 'discrepant analysis'. Even if one employs a perfect test to resolve the discrepant results, discrepant analysis estimates of test sensitivity and specificity are still biased. Thus, this technique should not be adopted for evaluating the performance of a diagnostic test.

S194 Quality control of nucleic acid amplification methods

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Diagnostic tests based on nucleic acid amplification (NAA) are now generally applied in clinical microbiology laboratories. The sensitivity and specificity of the NAA-based tests provide a powerful tool for rapid detection, identification and quantification of microorganisms. However, especially when low numbers of organisms have to be detected, false-negative and false-positive results may occur and the reliability of the methods is sometimes questionable. Quality control